Final Report

Project A01057

Assessment of the potential use of nanomaterials as food additives or food ingredients in relation to consumer safety and implication for regulatory controls

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July 2007

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Executive Summary

1. This study has been undertaken by the Safety of nanomaterials Interdisciplinary Research Centre (SnIRC), led for this study by Central Science Laboratory. The main aims of the study were to collate information on the current and projected use of nanomaterials as food additives or food ingredients, and to identify potential implications for consumer safety and regulatory frameworks.
2. Current applications of nanotechnology for food include nano-sized carriers for nutrients and supplements, nano-sized or nanoencapsulated food additives, and nanostructured food ingredients. The currently available examples of these include nutritional supplements and nutraceuticals, and a few food ingredients and additives.
3. At present, there is virtually all known nanotechnology-derived food product are available outside the UK/ EU. The only exception to this is a nano-micelle based carrier system for introduction of antioxidants in food and beverage products. The applications of nanotechnology for the food sector are, however, predicted to grow rapidly worldwide in the future, and it is widely expected that such applications will start to emerge on the UK/ EU markets in the next few years.
4. Most nanotechnology applications in the food sector seem to have emerged from similar developments in related sectors such as medicine, cosmetics, and nutraceuticals. Nanoencapsulation of food additives is a logical extension of microencapsulation technology that has already been used by the food industry for a number of years.
5. The applications of nanotechnology are likely to bring enormous benefits to the food and health-food sectors in terms of new tastes, flavours, textures, increased nutritional value, less fat and preservatives, maintenance of quality and freshness, better traceability and safety of food products.
6. There is a growing body of scientific evidence, which indicates that engineered free nanoparticles can cross cellular barriers, and that exposure to some forms may lead to increased production of oxyradicals and consequently oxidative damage to the cell. However, only a few studies have so far been carried out into the toxicology of nanoparticles, and much of the published research relates to exposure through inhalation.
7. This study has highlighted major gaps in knowledge that require further research to establish whether the consumption of nanofoods may lead to any consumer health implications. For example, research is needed into physicochemical properties, behaviour, fate and effects of manufactured nanoparticles used as food additives or ingredients.
8. There are uncertainties in current regulatory frameworks in relation to nanofoods that need appropriate amendments. For example, relevant definitions of novel food need clarifying in relation to nanotechnology derived food. Similarly, the use of food additives already approved for use needs revisiting if their nano-forms are used to allow testing of any potential changes in physicochemical properties, absorption, bioavailability, and health effects that may have a bearing on their permissible limits in food.
9. It is likely that the application of nanotechnologies in agriculture and food will attract significant public concern in the coming years. The report therefore recommends opening up a dialogue with key stakeholders, e.g. through a workshop and formation of a forum to help industry to identify and self-regulate the relatively high-risk applications of nanotechnology.

1.0 Introduction

The advent of nanotechnology, that involves manufacture and use of materials in the size range of up to 100 nanometres, has opened up a way for a multibillion dollar global industry in recent years. The market impact of nanotechnology is widely expected to reach 1 trillion US$ by 2015, with around 2 million workers (Roco and Bainbridge, 2001). Whilst the majority of manufacturing and use of nano-scale materials occurs in the United States, the European Union (EU), with its 30% global share of this sector, is not lagging far behind. Within the European Union, the UK accounts for nearly a third of the sector (Chaudhry *et al*., 2005; Aitken *et al*., 2006). A variety of consumer products that contain nanomaterials are already available in the UK and the EU. Examples of these are self-cleaning glass, anti-microbial wound dressing, paints and coatings, fuel catalysts and cosmetics[1].

The applications of nanotechnology in the food sector are relatively new emergent, but they are predicted to grow rapidly in the coming years. This is because food industry has always been looking out for new technologies to improve the nutritional value, shelf life, and traceability of food products, and to provide new tastes, flavours, textures etc. A number of new processes and materials derived from nanotechnology can provide answers to such needs. For example, increasing nutritional value, development of new tastes and sensations, and creamier textures through nanostructuring of food ingredients with much less (or no additional) fat. It is therefore not surprising that one of the fastest moving sectors to embrace new technologies to realise the potential benefits is the food industry. Many of the world's largest food companies have been reported to be actively exploring the potential of nanotechnology for use in food or food packaging[2,3].

The main developments in nanofood[4] area have so far been aimed at altering the texture of food components, encapsulating food components or additives, developing new tastes and sensations, controlling the release of flavours, and/or increasing the bioavailability of nutritional components. Many of the current nanotechnology applications in food appear to have emerged from similar technologies being developed for related sectors, such as pharmaceutical, cosmetics and nutraceuticals. The boundaries between food, medicine and cosmetics, are already obscure, and the advent of nanomaterials, which can interact with biological entities at a near-molecular level, is likely to further blur these boundaries. Some food and cosmetic companies are known to be collaborating to develop cosmetic nutritional supplements (Cientifica, 2006).

The rapid proliferation of nanotechnologies in a variety of consumer products has also raised a number of safety, environmental, ethical, policy and regulatory issues (Royal Society and Royal Academy of Engineering, 2004; Maynard et al., 2006, ETC Group[5]). The main concerns stem from the lack of knowledge in relation to the potential effects and impacts of nano-sized materials. The food applications of nanotechnology are likely to attract a significant public concern because of the potential risk of exposure of wider general public to nanoparticles.

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[1] The Woodrow Wilson Nanotechnology Consumer Products Inventory www.nanotechproject.org/consumerproducts (accessed January 2007)

[2] Cientifica 'Nanotechnologies in the Food Industry', published August 2006; www.cientifica.com/www/details.php?id=47

[3] 'Quietly, nanotechnology joins the food chain': The Sunday Telegraph, 22 October 2006, page 5.

[4] The recently coined term 'Nanofood' refers to the use of nanotechnology techniques, materials or tools during production, processing, or packaging of food.

[5] Down on the farm: the impact of nano-scale technologies on food and agriculture www.etcgroup.org/upload/publication/80/01/etc_dotfarm2004.pdf

1.1 Objectives

The current study was undertaken to meet the following objective:

- to collate and assess information in relation to the current and projected use of nanomaterials as food additives or food ingredients;
- to assess the potential hazards that might be associated with the nano-sized food additives or food ingredients;
- to assess the likely implications of the use of nano-sized food additives or food ingredients in terms of consumer safety and current regulatory controls in the UK; and
- to identify any gaps in knowledge and regulations, and to provide guidance on the needs for future R&D, and any needs for supporting (new or adjusted) regulatory frameworks.

1.2 Methodology

As part of this study, an extensive search for relevant information was carried out. The main sources of information for this review were:

- Extensive searches of published literature, relevant company websites, and different patent databases for nanomaterials or nanoparticles for their potential uses in food and drinks industry, and for any consumer safety implications.
- The international inventory of nanotechnology consumer products developed by the Woodrow Wilson Institute[1] for information on the available consumer products in the food and drinks sector.
- The Defra/ CSL database of nanomaterials manufactured and used in the UK: (http://nanotech.csl.gov.uk/) for information on relevant materials/ applications.
- A recent Market Analysis Report from Cientifica 'Nanotechnologies in the Food Industry'[2], published in August 2006.
- Key scientific reports, such as by Joseph, T. and Morrison, M. (2006) Nanotechnology in Agriculture and Food: A Nanoforum report (www.nanoforum.org), published by the Institute of Nanotechnology, and Scientific Status Summary on the Applications of Nanotechnology in the Food Industry, published by the Institute of Food Technologists (Weiss et al., 2006)
- Up-to-date information through discussions with international experts at the first European International Workshop "*Nano and Micro Technologies in the Food and HealthFood Industries'*, Amsterdam; the "*Nanotoxicology Conference"*, April 2007, Venice, Italy; and the "*2007 CSL/JISFAN Joint Symposium on Food Safety and Nutrition – Nanotechnology in Foods and Cosmetics"*, June 2007, Greenbelt MD, USA.

2. 0 Current status and future trends of the products and applications of nanotechnologies for food additives and food ingredients

It is clear from a number of reports, reviews, patents, and company products that nanotechnology applications have started to make an impact on different aspects of the food and associated industries (Chen et al., 2006). The nanofood sector is currently led by the

USA, followed by Japan and China; but Asian countries (led by China) are expected to be the biggest market for nanofood by 2010 (Helmut Kaiser Consultancy report)[6].

Estimates of the current global market size and the number of companies involved in nanofood sector are varied because of the difficulties in obtaining the exact information due to commercial and environmental sensitivities. Such sensitivities have led major food corporations, who had been, until a few years ago, at the forefront of food nanotechnology R&D, to disassociate themselves from publicity in this field, and become very protective of their activities in this area. Some Non Governmental Organisations, like the ETC Group, have called for a moratorium on the use of nanotechnologies in food products, until they are proven to be safe to consumers[5]. This has made the task of information gathering a very challenging one. Furthermore, much of the available information is aimed at projecting the 'magic' of nanotechnologies when applied to food, rather than 'real' products and applications that are available now or in a few years time. This study has therefore scrutinised the information objectively to separate facts from fiction, and has separated those products and applications that are identifiable from those that are merely anticipated[7].

It has been suggested that the number of companies currently applying nanotechnologies to food could be as high as 400 (Cientifica). A number of major food and beverage companies are reported to have (or have had) an interest in nanotechnology. These include Altria, Nestle, Kraft, Heinz, and Unilever, as well as small nanotech start-up companies (Cientifica, 2006). Other names of major food companies have been mentioned on different websites[8], but it is not clear how accurate this information is. It is, however, widely anticipated that the number of companies applying nanotechnologies to food will increase dramatically in the near future.

This study has indicated that virtually all known applications of nanotechnologies in food are currently outside the UK, mainly in the USA, Australia, and Israel. The information gathered as part of this study has not identified any UK or EU food company that has declared, or is currently known to be, using nanofood ingredients or additives in their products. The only exception to this is a nano-micelle based carrier system (Novasol® marketed by Aquanova® Germany) for introduction of antioxidants in food and beverage products (section 2.1). A health supplement based on Aquanova's technology (Nutri-Nano^{TM} CoQ-10 from Solgar, USA), claimed for increased absorption of the fat soluble CoQ-10, through conversion into water soluble micelles (~30 nm size), is currently being marketed in the UK[9]. The Aquanova website also indicates that Degussa have the rights for marketing micelles containing lipoic acid, although it is not clear whether this product is currently on the EU market.

The predictions for the future growth of nanofood market are also varied, partly due to the lack of exact information and a number of other factors that might affect the future success of nanofood products. A recent report by Helmut Kaiser Consultancy estimated that the nanofood market would have grown to US$7 billion in 2006, and will reach US$20.4 billion by 2010[5]. Another report by the consulting firm Cientifica has estimated the then current (2006) food applications of nanotechnologies were valued at around $410m (food processing US$100m, food ingredients US $100m, and food packaging $210m). According to the report, the current applications are mainly for improved food packaging, with some applications for delivery systems for nutraceuticals. The report estimated that by 2012 the

[6] Helmut Kaiser Consultancy. 2004. Study: nanotechnology in food and food processing industry worldwide 2003–2006–2010–2015 www.hkc22.com/Nanofood.html (accessed February 2007)

[7] 'It may be promising one day to make food from component atoms and molecules, the so-called "Molecular Food Manufacturing'; a quote from Cientifica report 2006

[8] e.g. http://online.sfsu.edu/~rone/Nanotech/atomicrice.htm (accessed January 2007)

[9] http://www.solgar.co.uk/modules/shop/view.asp?catid=18&Prodcode=E916 (accessed 23/07/2007)

overall market value would reach $5.8 billion (food processing $1303m, food ingredients $1475m, and food safety $97m, and food packaging $2930m).
Considering such rapid developments in this field, and the global setup of major food companies, it is not unreasonable to anticipate that nanofood products will start appearing on the UK/ EU markets within the next few years.

The current study has identified the following main categories of known and projected applications of nanotechnology in food, that need consideration in relation to consumer safety and regulatory implication:

- Where food ingredients have been processed or formulated to form nanostructures;
- Where nano-sized, nano-encapsulated, or engineered nanoparticle additives have been used in food;
- Where food may be contaminated indirectly through migration of nanoparticles from packaging, through contact with active surfaces, or the use of nano-sized agrochemicals, pesticides, or veterinary medicines.

This study has, however, not considered certain applications that are less likely to raise consumer safety issues. For example, nanofiltration for use in the removal of undesirable components in food, or food safety and security where nanotechnologies (e.g. nanosensors) have been used for the detection of food ingredients, additives, or contaminants.

In terms of R&D activities in the area of nanofood, it has been estimated that over 200 companies worldwide are conducting R&D into the use of nanotechnology in engineering, processing, packaging or delivering food and nutritional supplements[5,10]. Whilst a handful of food and nutrition products containing nano-additives are already commercially available, e.g. synthetic lycopene (BASF), over 150 applications of nanotechnology in food are reported to be at different stages of development (Cientifica, 2006).

The search of patent databases for this study found a total of 464 patent entries with regard to applications of nanotechnology in food or food contact materials. Of these, patents relevant to nanofood applications were selected and examined in more detail. A brief listing of relevant patent applications is provided in Table 1.

The R&D activities in the area of nanofood, which provide an insight to future developments, are mainly aimed at:

- Improving the appearance of food, e.g. by altering colour, flavour, texture, consistency, and developing new tastes and sensations in the mouth;
- Controlling the release of flavours and nutrients, and enhancing the absorption of nutrients and nutraceuticals in the body;
- Reducing the amount of fat, colour, preservatives to promote healthy option foods;
- Removing undesirable compounds from foods through nanofiltration; incorporating nanosensors in food packaging for traceability and food safety

A number of current R&D developments are in the areas of nutraceuticals, interactive or functional foods. These include the use of food as a means to enhance nutrition, beauty (the concept of ‘beauty from within’), well-being; and enabling consumers to modify food depending on their nutritional needs or tastes. One example of the latter is a colourless and tasteless beverage that will contain nanoencapsulated ingredients or additives that can be activated by a consumer at a particular microwave frequency. This would lead to activation of selected nanocapsules whilst the others remain latent, releasing only the preferred

[10] Institute of Food Science and Technology (IFST) Trust Fund. 2006. Nanotechnology information statement www.ifst.org/uploadedfiles/cms/store/attachments/nanotechnology.pdf

flavour, colour or nutrients (Cientifica, 2006). Some major food companies are reported to be developing new nanomaterials to extend food shelf life and signal when a food spoils by changing colour. Another area under current R&D is the development of active and self-cleaning surfaces for the food industry.

The prominent institutions and networks with interests in different aspects of nanofood include:

- Denmark's Center for Advanced Food Studies (LMC), an alliance of Danish institutions working in food sciences, and aiming to manufacture nanomaterials with functional properties, along with nanosensors and nanofluidic technology for applications in food sciences.
- Wageningen Bionanotechnology Center at Wageningen University (The Netherlands) that focuses its research on the application of nanotechnology in the food industry. Projects include assembly of food proteins into microfibrils, and the use of drug delivery systems for delivery of nutrients.
- NanoteK Consortium, USA: In 2000, Kraft Foods launched the NanoteK Consortium of research groups from 15 universities, 3 national labs and 3 start-up companies to explore the applications of nanotechnologies to make interactive foods. The consortium planned to develop smart foods that release nutrients in response to deficiencies detected by nanosensors, and nanocapsules, which will be ingested with food, but stay latent until activated.
- Nanofood Consortium. A cluster of scientists from Northern European food industries looking to nurture applications of nanotechnology in the food industry, to develop healthy and safe foods, to develop sensors for toxic compounds or bacteria in food products; anti-bacterial surfaces for food production machines; thinner, stronger and cheaper wrappings for food; and food with a healthier nutritional composition.
- Leatherhead Food International has recently formed a new working group 'NanoWatch' to investigate the use of nanotechnology in the food and drink industry, with particular emphasis on ingredients and hydrocolloids.

2.1 Examples of nanotechnology applied to the area of food ingredients

The nanostructured (or nanotextured) food ingredients are being developed with the claims that they offer improved taste, colour, flavour, texture, and consistency. Another claim being projected in relation to nanostructured foods (e.g. mayonnaise, spreads, ice-creams) is that they will have a creamy texture with much less (or no additional) fat, and hence will offer a healthier option. The processes commonly used for producing nanostructured food products include nano-emulsions, surfactant micelles, emulsion bilayers, double or multiple emulsions and reverse micelles (Weiss et al., 2006). This study found no clear example of a nanostructured food product that is currently available on the UK/ EU market. There are, however, a variety of nano-micelle based supplements and nutraceuticals that are available in some countries[1]; for example:

- Novasol® from Aquanova® (Germany) is a nano-micelle based carrier system, which is claimed to help manufacturers introduce antioxidants into food and beverage products.
- Nano-structured supplements based on 'Nano-Sized Self-assembled Liquid Structures (NSSL)' from NutraLease Ltd. (Israel). Acting as carriers for targeted compounds (e.g. nutraceuticals and drugs), these nano-sized vehicles comprise expanded micelles in the size of ~30 nm. One example of available products is

'Canola Active Oil' by Shemen Industries, Israel. The oil contains NSSL-based nano-micelle carrier claimed for increased penetration of vitamins, minerals and phytochemicals.

- NanoCluster™ delivery system for food products from RBC Life Sciences® Inc. (USA). The available products include Nanoceuticals™ Artichoke Nanoclusters, Nanoceuticals™ Spirulina Nanoclusters, and Nanoceuticals™ Slim Shake Chocolate that contain cocoa nanoclusters claimed to offer enhanced flavour.
- BioDelivery Sciences International's Bioral™ nanocochleate nutrient delivery system, for micronutrients and antioxidants. This phosphatidylserine based carrier system (~50nm) is derived from soya bean, generally regarded as safe (GRAS).
- Self-assembled nanotubes from hydrolysed milk protein α-lactalbumin with a good stability have recently been developed (Graveland-Bikker and de Kruif 2006). σ-lactalbumin is already used as a food ingredient, mainly in infant formula. These food-protein derived nanotubes may provide a new carrier for nanoencapsulation of nutrients, supplements, and pharmaceuticals.

2.2 Examples of nanotechnology applied to the area of food additives[11]

The use of microencapsulated additives in food is already well established. For example, microencapsulion has been used to mask the taste and odour of tuna fish oil, added to bread for health benefits (e.g. 'Tip Top-up' brand bread from George Weston Foods, Australia). A variety of other microencapsulated food ingredients and additives are available for use in a range of food products (e.g. PrimeCAP® from Prima Foods Corporation[12]). A recent trend in microencapsulation is that of live probiotic microbes[13]. In this context, the nano-encapsulation of food ingredients and additives appears a logical extension of the technology into an already existing application area to provide protective barriers, flavour and taste masking, controlled release, and better dispersability for water-insoluble food ingredients and additives.

Most nano-sized or nanoencapsulated health supplements and nutraceuticals are claimed for enhanced absorption and bioavailability in the body. A number of products containing nano additives (e.g. vitamins, nutraceuticals, antimicrobials, antioxidants, flavourings, colorants, preservatives etc) are available on the market in some countries. A few examples of these are given below, whilst many more are likely to be under development (Cientifica, 2006).

- The Nanoceuticals™ range of products from RBC Life Sciences® Inc. (USA); such as Microhydrin® and Microhydrin® Plus that contain nanocolloidal silicate mineral, claimed to neutralise free radicals; and Hydracel® claimed to lower the surface tension of drinking water and hence increase solvent properties.
- Nano Calcium/Magnesium from Mag-I-Cal.com (USA), claimed to allow greater absorption and bioavailability of calcium/ magnesium in the body.
- Nutri-Nano™ CoQ-10 from Solgar (USA), claimed for increased absorption of the fat soluble CoQ-10 through conversion into water soluble micelles (~30 nm size).

[11] The wording and the claims are taken from the references

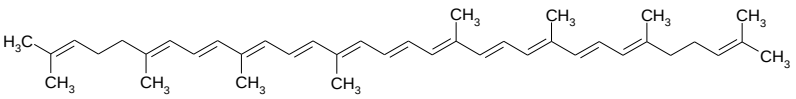
[12] www.primerafoods.com/primecap.asp

[13] One example is Living Fuel Rx's CocoChia snack bar that is claimed to contain stabilised microencapsulated probiotics www.livingfuel.com/LFP_07.htm (accessed February, 2007)

- C.L.E.A.N. Products from SportMedix, Inc. (USA) nano-structured bioregulators, claimed to control biological processes responsible for normal functionality of organs and tissues.
- LifePak® Nano, a nutritional anti-aging formulation from Pharmanex® (USA), claimed for increased bioavailability of components to nourish and protect cells, tissues, and organs in the body.
- Nanotea from Shenzhen Become Industry & Trade Co., Ltd. (China)[14]. This nano-selenium rich tea claims greater bioavailability of selenium, which is claimed for a number of health benefits.
- Nano B-12 Vitamin Spray by Nutrition from Nanotech, LLC (USA), the nano-droplets are claimed to designed to release the vitamin within a steady, time-controlled manner, whilst enhancing efficiency.

2.2.1 Example of an organic nanoparticulate food additive[11]

BASF *US Patent US5968251 Production of carotenoid preparations in the form of coldwater-dispersible powders, and the use of the novel carotenoid pigments*[15]



Chemical structure of lycopene

These products are formed by:

(a) Preparing a molecular-disperse solution of a carotenoid e.g. lycopene, a natural antioxidant, with or without an emulsifier and/or edible oil, in a volatile, water-miscible organic solvent at elevated temperature and adding therein an aqueous solution of a protective colloid. The hydrophilic component is then transferred into the aqueous phase leaving the hydrophobic phase of the carotenoid as a nanodisperse phase.

(b) Heating the resulting hydrosol at 40-90°C, with or without cooling of the hydrosol to 0-30°C beforehand, and

(c) Removing the solvent and the water from the heated hydrosol and converting it into a water-dispersible dry powder *ca.* 100 nm in size.

The insolubility of carotenoids in water, moderate solubility in fats and oils and susceptibility to oxidation impede the direct use of relatively coarse particles, which also limits their colouring ability. The processes described in (a)-(c) above result in a nanoparticulate active substance dispersion that is distinguished by its absorption spectrum, yellow-orange hue and all-*trans* isomer content of *ca.* 76%, which may be reduced upon exposure to high temperatures with concomitant increase in *cis*-isomers content. The technological requirements are particularly high for carotenoid use in the colouring of aqueous media,

[14] www.369.com.cn/En/nano.htm

[15] BASF Production of carotenoid preparations in the form of coldwater-dispersible powders, and the use of the novel carotenoid pigments US Patent US5968251. www.freepatentsonline.com/US5968251.html.

however the nanoparticulate nature of the products described are stated to realise a wide diversity of colouring properties associated with improved bioavailability.

Examples of carotenoid permitted food colourings which can be employed in this type of product are well characterised, widely available and occur in both natural or synthetic forms e.g. β-carotene (E160a), bixin (E160b), β-apo-8'-carotenal (E160c), lycopene (E160d) and the ethyl ester of β-apo-8'-carotenoic acid (E160f). Water-miscible, thermally stable, volatile solvents containing only carbon (< C_{10}), hydrogen and oxygen, such as alcohols, ethers and acetone are used preferably. Examples of protective colloidal substances include dextrin (E459), gum Arabic (E414), modified starch (E1450), pectin (E440) and gelatin. It is also possible to employ cellulose and its derivatives (E460-469) as well as alignates. To increase the mechanical stability of the final product, plasticizers such as sugars and sugar alcohols are added e.g. sucrose, glucose, lactose, invert sugar, sorbitol (E420), mannitol (E421) and glycerol (E422). The weight ratio of protective colloid and plasticizer to the carotenoid solution is ca. 0.5-20% carotenoid, 10-50% protective colloid and 20-70% plasticizer.

To increase the stability of the active substance(s) against oxidative degradation, stabilizers are added such as □-tocopherol (E307), BHA (E320), BHT (E321), ascorbic acid (E300) or ethoxyquin. These can be added either to the aqueous or solvent phase, but are usually mutually dissolved with the carotene, with or without emulsifiers, in the solvent phase. Examples of emulsifiers include ascorbyl palmitate (E304), polyglycerol fatty acid esters (E475), sorbitan fatty acid esters (E491-495), propylene glycol fatty acid esters (E477) and lecithin (E322). These are added at a relative concentration of 0-200% (preferably 20-80%) to the weight of the carotenoid(s). The main foodstuff applications are soft drinks, baking mixtures and blancmanges but this is predicted to expand in scope significantly.

2.2.2 Example of a manufactured inorganic nanoparticulate food additive[11]

Mars Inc. US Patent US5741505 nanoscale inorganic coatings[16]

This is an example of inorganic nanoscale coatings used to provide moisture or oxygen barriers and thereby improve shelf life and/or the flavour impact of foods. The materials used for the coatings include the permitted additives silicon dioxide (SiO_2, E551), magnesium oxide (MgO, E530) and titanium dioxide (TiO_2 E171), which are preferably insoluble. The coating is applied using a continuous process as a thin amorphous film of 50 nm or less to prevent cracking of the barrier if the product is flexed. The flexibility of the coatings may be increased by the addition of other additives during production. The technological advances gained from the use of such products are achieved without greatly affecting the desired organoleptic qualities of the product. Specific applications include:

- Low moisture foods requiring expensive moisture barrier protection to prevent them becoming soggy; ready-to-eat cereals that when served in milk become soggy with time
- Hard sugar confectionery that becomes sticky when exposed to high humidity
- Biscuits and crisps that become soggy or stale when the packaging is opened or when stored for a prolonged period
- Display food products requiring long shelf lives, which may discolour or crack due to moisture loss

[16] Mars Inc. Edible products having inorganic coatings. United States patent 5741505. www.freepatentsonline.com/US5741505.html.

- Confectionery items with coloured sugar coatings, which rub off onto hands; air and humidity solubilises the coating sugars that carry the colouring
- Low-fat systems in which water replaces fat but which dry out over time thereby limiting shelf life
- Oxygen-sensitive systems containing nuts or milk fat that becomes rancid with time as oxygen migration, and thus lipid oxidation are increased

The manufacturers state that the coating should be at least 80% pure but preferably 90% or more. SiO_2 is considered to be particularly advantageous because it is an EU-approved anti-caking agent that may be used up to 1% by weight. TiO_2 is a colouring material permitted under Annex V of European Parliament and Council Directive 94/36/EC[17]. Source compounds for SiO_2 used in the production of the nanoscale SiO_2 coatings include organosilicates, silanes, chlorosilanes and tetraethylorthosilane (TEOS). The EU purity specification for TiO_2 contains no reference to limits on particle size[18].

Another example of manufactured inorganic nanoparticlulate material is nanosilver, which has been suggested for incorporation as a health supplement or food additive for natural antimicrobial action. The use of colloidal silver has also recently appeared in a wide range of medical applications, cosmetics and personal care products, and food packaging materials. Colloidal silver formulations are now available from a number of sources, and its use in health foods and supplements is likely to rise in the future.

2.2.3 Example of a nano delivery system for nutrients

BioDelivery Sciences International nanocochleate delivery system [19]

The BioDelivery Sciences International (BDSI) Bioral™ nanocochleate[20] is a nutrient delivery system for protecting micronutrients and antioxidants from degradation during manufacture and storage. This is achieved using phosphatidylserine carrier derived from soya beans and generally regarded as safe (GRAS), in the form of a nanoscale cochleate. The Bioral™ nanocochleates can be as small as 50 nm in diameter, comprising a crystalline latticework with an anhydrous interior. The nanocochleates are resistant to heat, pH, hydrolysis and oxidation. It is interesting that one of the claimed clinical properties of the nanocochleates is the ability to fuse readily with cell membranes. This is reported to result in a relatively high intracellular concentration compared to that in blood. The manufacturers also claim an 'increased therapeutic index' with a innocuous metabolic byproduct not described in the literature source used[19]. Delivery applications include carotenoids, vitamins, omega-3-fatty acids, polyunsaturated fatty acids, and phytochemicals such as phytoestrogens and related polyphenols. Other functional applications of the nanochelates include the masking of aromas and flavours.

The Bioral™ nanocochleate nutrient delivery system is claimed to have enabled the addition of Omega-3 fatty acids for use in goods that are then baked or cooked such as cakes, muffins, pasta noodles, soups, and cookies. BDSI has also claimed to have added the Bioral™ Omega-3 formulation to soy milk, milk, liquid yoghurt, orange juice, smoothies,

[17] European Parliament and Council Directive 94/36/EC

[18] Commission Directive 2006/33/EC

[19] Bioral processed Foods and Products. Bioral ™ nutrient delivery for fragile micronutrients. www.biodeliverysciences.com/bioralnutrients.html.

[20] Addition of calcium ions to small phosphatidylserine vesicles induces formation of discs that are fused into large sheets of lipid, and rolled up into nanocrystalline structures, termed "cochleates," after the Greek name for a snail with a spiral shell.

sports drinks, soft drinks, coffee, frappuccinos, and other beverages without altering taste or odour. Other potential applications include manufacturers' inclusion in cereals, chips, and candy bars. Moreover, BDSI has added the Bioral™ Omega-3 formulation to soy milk, milk, liquid yoghurt, orange juice, smoothies, sports drinks, soft drinks, coffee, frappuccinos, and other beverages without altering taste or odour.

3.0 Physicochemical nature of nanomaterials used in foods

The currently available information suggests that both organic and inorganic nanomaterials have been used as food additives. From the examples given in Section 2.2, the organic food additive Lycopene (BASF) is a carotenoid nanomaterial with particle size in the range of 100 nm. The materials for coating of confectionary products (Patent application by Mars Inc.) include the permitted additives silicon dioxide (SiO_2, E551), magnesium oxide (MgO, E530) and titanium dioxide (TiO_2 E171), which are preferably insoluble. The coating is applied using a continuous process as a thin amorphous film of 50 nm or less.

The Bioral^{TM} nanocochleate delivery system contains phosphatidylserine carrier that can be as small as 50 nm in diameter, comprising a crystalline latticework with an anhydrous interior.

The diameter of nano-micelle based carrier system Novasol® (marketed by Aquanova® Germany) for introduction of antioxidants in food and beverage products is approximately 30 nm.

More details on other nanostructured food ingredients is currently not available, but it is anticipated that the average particle size will be up to 100 nm (to fulfil the current definition of a nanomaterial).

4.0 Potential Hazards Associated with Nano-sized Food Ingredients and Additives

It is known that materials manufactured at nano-scale may have substantially different physicochemical and biological properties from their conventional forms. This is because conventional physicochemical rules are not as well understood at the nanometer scale. Depending on physicochemical nature of the material, quantum effects may have a much greater influence on the properties of a nanomaterial compared to larger particles. Also, on a weight per weight basis, nanomaterials have much larger surface areas compared to say, microparticles (10^{-6}m).

Very few studies have been carried out so far into the toxicology of nanoparticles, and much of the published research relates to inhalation exposure. The potential effects of nanoparticles through the gastrointestinal route are largely unknown. The application of nanotechnology in food has, therefore, led to concerns that ingestion of nanoparticles may pose unforeseen health or environmental hazards. Such concerns have arisen from a growing body of scientific evidence which indicates that free nanoparticles can cross cellular barriers, and that exposure to some engineered nanoparticles can lead to increased production of oxyradicals and consequently oxidative damage to the cell (Oberdörster, 2000; 2004; Donaldson et al., 2002; 2004, Tran et al., 2005).

However, despite the potential of some nanoparticles to cause harm, the likelihood and extent of human exposure through consumption of nano-foods and drinks is currently unknown. Some engineered nanoparticles, such as nanosilver, are known to have strong antimicrobial activity, but at present there is no published research on their potential effects on the gut natural microflora. There is, therefore, a need for research to establish the facts and remove uncertainties in relation to the potential hazards and likelihood of exposure to nanoparticles through consumption of nanofoods.

5.0 Potential Consumer Safety Issues Arising from Nanofoods

In the UK, the median adult intake of fine particles via inhalation is in the region of 10^{12} - 10^{13} microparticles/ individual per day (Tran et al 2005). The main likely route of entry of micro- or nano-sized particles to the gut is through consumption of food and drinks. However, very little is known about the dietary toxicity of microparticles in the gut, and even less about the toxicity of nanoparticles (Tran et al, 2005). The main consumer safety concerns from the application of nanotechnologies in food are also intrinsically linked to the physicochemical nature of the nanoparticles, and the likelihood and extent of exposure through consumption of nanofoods.

It is known that some food substances exist naturally, or are metabolised in the body at a nano-scale. Many food proteins are globular structures, reported to be between 10's to 100s nm in size, and most polysaccharides and lipids are linear polymers less than 2 nm in thickness[21]. The main concern in this regard is that processing of food ingredients to make them nano-sized may make them different from those that exist naturally.

A healthy digestive system only allows absorption of nutrients from the gut after digestion of foods. The gut wall is designed to ensure the passage of dietary nutrients, and prevent the passage of larger or foreign material. The transport of conventional forms of nutrients (and metabolites) in and out of the cell is also well regulated in the body. Nano-sized food ingredients and additives may, however, 'override' these mechanisms due to ability to cross the gut wall, and this may lead to health implications for the consumer (see section 5 for further discussion). There is potential for contamination of food with nanoparticles, e.g. from the use of nano- pesticides and veterinary medicines, or migration of nanoparticles from food packaging. It is also not known to what extent nanoparticles in the environment would bioaccumulate/ bioconcentrate in the food chain.

A number of possible implications may be envisaged to emerge from the consumption of nano-sized food ingredients and additives. For example, a greater absorption of certain nano-ingredients may change nutrient profile in the body, or a greater absorption of nano-additives may lead to increased health consequences. As behaviour, fate and effects of nanoparticles are currently not fully understood, there may be other unforeseen implications that may jeopardise consumer safety.

5.1 Nanosized ingredients and additives in relation to digestion of food

The three main constituents of food; proteins, carbohydrates and lipids are each digested in a different manner (see Table 2). However, a common factor between the three is that digestion of their constituents occurs at the nanoscale. Based on this, it could be argued that the processing of foods at the nanoscale would simply improve the speed or efficiency of their digestion, uptake, bioavailability and metabolism in the body. Indeed, within the nutrition market there are already supplements that claim to contain di- and tri- peptides, and are thus more readily digestible (Crisalle, 2007). In contrast, it could be argued that since the processing of substances to this scale often alters their properties, then nano-scale processing of foods may alter how the food ingredients `behave' upon breakdown within the gut, and as a consequence how they are treated in the gastrointestinal tract. This is an important aspect that needs further research, as it will provide answer to an important regulatory question, i.e. should a nano-processed food be considered automatically a novel food due to significant changes in composition and properties?

The intestinal wall is folded into villi to maximise the surface area for digestion. The villi surface is composed of two main cell types: enterocytes (the majority) and goblet cells.

[21] www.ifr.ac.uk/publications/scienceinnovation/0502_nanotechnology/

Translocation of particles through the intestine depends on 4 main factors: 1. diffusion and accessibility through mucus lining the gut wall, 2. initial contact with enterocytes or M-Cells, 3. cellular transport, 4. post-translocation events (Hoet et al 2004).

5.2 Translocation of particulates through intestinal Mucus

A mucus layer lines the epithelial cells of the gut wall. It is secreted by goblet cells, one of two principal cell types found in the intestinal wall. Mucus is principally composed of proteins (called mucins) within an electrolyte suspension (des Rieux *et al*, 2006) and helps to trap pathogens and remove foreign materials before they come into contact with the gut epithelium. Passage of particulates through the intestinal mucus is dependant on multiple factors, two of these being particle size and charge.

The mucus lining the gastrointestinal epithelia forms a mesh-like barrier through which it was originally thought that passage of molecules over ~55 nm in diameter was prevented. This ensured that only small molecules could access the villi of the gut epithelium for digestion. It has also been demonstrated that smaller particles are able to diffuse through the mucus layer faster than larger particles (Szentkuti, 1997).

Passage of particles through intestinal mucus is also dependant on surface charge. Szentkuti (1997) showed that particles of various sizes and charges diffused through intestinal mucus at differing rates. Cationic nanoparticles were found to become entrapped within the negatively charged mucus, whereas carboxylated (anionic) microparticles were able to diffuse successfully through to the epithelial surface.

It has recently been discovered that pores within the mucus layer are much larger than originally anticipated. Researchers at the John Hopkins University, Maryland have recently published evidence to suggest that particles as big as 200 nm can pass through mucus pores when coated with polyethylene glycol (a substance used commonly to coat drug particles and to prevent uptake by phagocytic immune cells) (Samuel et al., 2007). This was due to the neutral surface charge of the particles coated with polyethylene glycol.

5.3 Contact with enterocytes and M cells

Absorption of food occurs mainly through enterocytes situated on the villi of the gut wall epithelium. Enterocytes serve two main functions - to control passage of macromolecules and pathogens, and to allow absorption of dietary constituents.

Contained within both intestinal mucus and gut wall epithelium are aggregates of lymphoid nodules, commonly referred to as Peyer's Patches, and within the epithelium of Peyer's Patches are M Cells. These take in samples of foreign material and deliver them to underlying lymphocytes to elicit immune responses and thus control disease (Berne and Levy 2000). It is here that foreign objects that have passed through intestinal mucus are usually accumulated.

Under normal circumstances, passage of particles through enterocytes takes place after foodstuffs have been digested into their constituents, and this process may be passive, facilitated, or active depending on the characteristics of the breakdown product.

5.4 Cellular translocation

Once food constituents have been broken down by enzymes, diffused through the gut mucosa, and absorbed through the enterocytes of the epithelia, they are translocated across the cells and pass into the hepatic circulation. There are several mechanisms by which particles may pass through the epithelia. These are - transcytosis by enterocytes (as with

normal digestion), transcytosis by M Cells (although this is more likely to lead to accumulation within M Cells, and a consequent immune reaction), passive diffusion across the epithelia or paracellular transport.

The time between the initial contact of particulates with the epithelial wall, to their absorption and translocation across cells is relatively slow. Szentkuti (1997) reported that accumulation of particles within the cell layer under the intestinal epithelium was still relatively low after several days of oral gavage of particles within rats.

Translocation through intestinal epithelia occurs by transcytosis through enterocytes. This is the basis of normal absorption (e.g. selective uptake of peptides or amino acids through transporters within the brush border), and it is well documented that gastrointestinal uptake of exogenous nanoparticles is greater than microparticles. Desai et al. (1996) showed that translocation of nanoparticles, 100 nm in diameter, is 15-250 times greater than that shown by micromolecules, which are more likely to become lodged within Peyer's patches (des Rieux et al 2006). The gastrointestinal uptake of nanoparticles has been shown to be 2-200 times greater on Peyer's Patches, despite the fact that these only represent ~1% of the total intestinal surface (des Rieux et al 2006).

Translocation of manufactured nanoparticles through the epithelium is likely to be dependant on the physiochemical properties of the nanoparticle e.g. zeta potential, hydrophobicity, size, presence/ absence of a ligand, and physiology of the intestinal tract e.g. healthy vs diseased state (where translocation may be increased or decreased depending on the illness) (des Rieux et al. 2006).

In relation to nanoscale processed foodstuffs, the issue of altered translocation arises only if the properties of the food's constituents are altered by processing. In addition, if engineered nanoscale additives or ingredients have been purposely introduced into the foods, or have migrated from packaging, their properties and potential effect on digestion must also be considered. In these cases, the 'novel' properties of each food would have to be determined in order to predict whether translocation would differ from the normal.

Under normal physiological conditions, paracellular transport of nanoparticles would be extremely limited, as pore size at tight junctions is between 3 and 10Å (0.3-1.0 nm) (des Rieux et al 2006). However, research into improving paracellular transport through gut epithelia is being carried out alongside medical research into targeted drug delivery. For example, research into using positively charged poly(acrylic) acids to aid nanoparticle passage via interaction with the negatively charged surface of the epithelium, or complexing Ca^{2+} involved in the structure of tight junctions (des Rieux et al 2006).

The behaviour and fate of nanoparticles in the gastrointestinal tract is, however, not known. It is possible that they will not remain in a free form (and hence not available for translocation) due to certain transformations in the gut, e.g. due to agglomeration, aggregation, adsorption or binding with other components of food, reaction with acid and digestive enzymes etc.

Any enhanced absorption and bioavailability of nano food ingredients and additives would give rise to higher internal exposure, with higher plasma concentrations (from higher absorption rate) or higher area-under-the-curve exposure (from higher uptake efficiency). This raises a number of questions with regard to consumer safety; for example:

- Would this alter the overall nutrient profile and nutritional status in the body?
- Should permissible limits be lowered for nano forms of food additives because of their greater absorption (and hence potential harmful effects) in the body?

Current understanding in this respect is limited. Further research would be needed to understand whether normal nutrient/ metabolite transport in and out of a cell is affected by introduction of a nano-food ingredient or additive.

5.5 The influence of particles in Disease

Investigation of the possible link between micro and nanoparticles and exacerbated symptoms in individuals with compromised gastrointestinal functionality (Irritable Bowel Disease (IBD) or Crohn's Disease) has led to the questions about whether the presence of dietary micro- and nano-particles may also elicit inflammatory responses in unaffected humans.

The modern Western diet means that the gut mucosa is continuously exposed to inorganic micro- and nano-particles. These dietary micro- and nano-particles may generally be grouped into three forms: natural contaminants (e.g. soil and dust), food additives, and those formed *de novo* from the environment or from the gut lumen (e.g. calcium phosphate) (Lomer et. al. 2001).

Micro- and nano-particles commonly found in food are typically oxides of silicon, aluminium and titanium (Powell et. al. 2000). For example, naturally occurring microparticulates such as titanium dioxide and aluminosilicates are used as food additives: titanium dioxide is present in anatase (E171), and aluminosilicates are commonly added to granular and powdered foods as anti caking agents (Lomer et. al 2001). These particles are highly stable, and are not degraded in the intestine. They are therefore typically taken up by M Cells of Peyer's Patches and passed to underlying macrophages. As macrophages are also unable to digest the particles, it is common to see pigmentation in cells at the base of human intestinal lymphoid aggregates due to particle accumulation (Powell et. al 2000). Concomitantly, both titanium dioxide (anatase) and aluminosilicate (as kaolinite) are commonly seen in these lymphoid aggregates (Powell et. al. 1996).

Studies so far have focussed heavily on microparticulates, and initial findings indicate that they appear not to be indicated as stimulants for Crohn's disease or IBD when presented alone. As the particles pass through the intestinal tract, they come into contact with, and adsorb luminal constituents, such as calcium ions and lipopolysaccharide. It has been shown that microparticle-calcium-lipopolysaccharide conjugate activates both peripheral blood mononuclear cells (Powell et. al 2000), and intestinal phagocytes, which are usually resistant to stimulation (Ashwood et. al 1999). This indicates that microparticles may be adjuvant triggers for exacerbation of disease within sufferers of Crohn's disease and IBD (Powell et. al. 2002, Lomer et. al. 2002). However, little is known about whether micro- or nano-particles are linked to the initiation of the diseases (Lomer et. al 2005, Powell, 2004).

Trials carried out so far to test whether reduction of microparticles in the diet
Can reduce the symptoms and Crohn's and IBD, have produced contradicting results. In a double blind randomised study, Lomer et al (2002) demonstrated that a particle-low diet alleviated the symptoms of Crohn's Disease. However, recent clinical findings have suggested that reducing microparticle intake in Crohn's sufferers has no effect on the disease (Lomer 2005). It is therefore evident that despite initial attempts to establish the presence or absence of a link between compromised functionality of the GI-tract and initiation or exacerbation of disease, there is a requirement for considerable further research. This avenue of research should, however, in time also uncover important information about the behaviour of micro and nanoparticles within the gastrointestinal system.

6.0 Adequacy of relevant regulations and implications of the use of nanomaterials in foods and food products

The Food Standards Agency (FSA) has recently published a (draft) review that considers the regulatory implications and risk assessment in relation to applications of nanotechnologies in food (Draft report of FSA regulatory review, 2006). Another regulatory gap study by

Chaudhry et al. (2006) has assessed existing regulatory frameworks relevant to food and food packaging along with a number of other known and projected products and applications of nanotechnologies.

It emerges from these reviews that most nanotechnology applications in food should come under some sort of approval process. The FSA (draft) review further concludes that the existing models for risk assessment should be applicable to nanomaterials, but there are major gaps in information on hazard and exposure.

This study has identified the main areas where there are uncertainties that might limit the scope and effectiveness of regulatory controls. For example:

- current legislation does not differentiate between 'conventional' and 'nano' forms of food additives already approved for use in food. There is currently no size limitation on particle size for food additives[22];
- there is a lack of clarity in the definition of novel foods under relevant regulations that may lead to uncertainty as to whether (and when) a food processed at nano-scale should be considered a novel food;
- there is a lack of knowledge of the effects of processes and products of nanotechnologies in food to enable adequate risk assessment.

6.1 Regulatory Aspects Relating to Nanoscale Food Additives

The use of food additives in the EU is controlled by European Parliament and Council legislation and is based on the principle that only additives that are explicitly authorised may be used in food. In addition, the quantities permitted are often limited and their use is restricted to specific foodstuffs in some cases.

Legislation relevant to nanoscale food additives is provided under Framework Directive 89/107 and the subordinate legislation. Nano food additives are assessed either as novel additives or, where a macro-equivalent is already approved, through potential amendments of the appropriate purity criteria under the Directive 96/77/EC.

Under the EC law, food additives are defined as substances that are not normally consumed as food itself, but are intentionally added to food for a technological purpose, such as food preservation. Substances that are used for the purpose of imparting flavour and/or taste are not considered food additives *per se* (separate legislation generally applies to these substances), and neither are substances that may be used for a technological function but are considered as food ingredients, such as sodium chloride or saffron. Prior to their authorisation by the Commission, food additives are evaluated for their safety by the European Food Safety Authority (EFSA). This role was previously the responsibility of the independent scientific committees, such as the Scientific Committee for Food.

In July 2006, the European Commission published a set of four proposed Regulations which are set to replace the current system and provide a common basis for controls on food additives, food flavourings and food enzymes. The proposals were published as Commission Documents on additives[23], flavourings[24], enzymes[25] and a common authorisation

[22] Particle size is only specified for E460 cellulose (crocrystalline), where smallest particle size should not get below 5 μm

[23] Additives: COM/2006/0428 final - Proposal for a Regulation of the European Parliament and of the Council on food additives {SEC(2006) 1040} {SEC(2006) 1041}

[24] Flavourings: COM/2006/0427 final - Proposal for a Regulation of the European Parliament and of the Council on flavourings and certain food ingredients with flavouring properties for use in and on

procedure[26]. The recently adopted proposals bring together all of the existing food additive regulations and propose to introduce comitology for additive approvals in place of the cumbersome co-decision procedure. Moreover, in line with the decision to separate risk assessment and risk management, all applications for the approval of new food additives will be directed to EFSA, which will carry out safety evaluations and risk assessment. At present this task would fall to the EFSA AFC Panel (Additives Flavours and Food Contact Materials). To date, EFSA has not announced if and how they may consider the issue of nanomaterials. The inclusion of a food additive in the Community positive list will be considered by the Commission on the basis of the opinion from EFSA. In addition to the safety of the substance, the other general criteria (technological need, consumer aspects) have to be examined before a food additive may be included in the Community positive list. This will be done by the Standing Committee on the Food Chain and Animal Health (SCFCAH).

For every authorised food additive included in the positive list, a specification must be laid down that contains the criteria on the purity and defines the origin of the food additive, and the verification of such criteria. The most relevant aspect in relation to the use of nanoscale food additives is perhaps in the re-evaluation of safety assessment. To ensure that food additives once permitted are kept under continuous observation and re-evaluation wherever necessary, producers or users of food additives will be obliged to inform the Commission of any new information which may affect the safety assessment of a food additive. These must include changing conditions of use and any new scientific information. Whether or not developments in nanotechnology constitute new scientific information may be for EFSA to assess in the first instance.

Food processing aids, interestingly, are not included within the scope of the proposed Regulation, which may have implication on the use of certain nanotechnologies, for example carrier systems used to protect additives during processing only under the auspices of novel foods. It is clear that food additives must at all times comply with the approved specifications. The specification should include information to describe *adequately* the food additive i.e. to ensure that in all relevant aspects it corresponds to the additive that has been assessed for safety. While existing food additive specifications are to be maintained until the corresponding additives are entered into the Annexes of the new Regulation, there are as yet no criteria within the specifications that cover the use of nanoparticles *per se*.

The definitions laid down in Article 3 of the proposed Regulation list certain substances that are not to be considered as food additives. Among these are substances that are mentioned in the examples given in section 2.2, which could lead to a greying of the distinctions e.g. certain types of dextrin and modified starches, gelatine, and products containing pectin.

In the example of an organic food additive (section 2.2.1), it may be envisaged that the nanoscale product might comprise a cocktail of additives that have been approved separately, each with a specification of purity that may include criteria for specific source materials. In the example of inorganic food additives (section 2.2.2), the purity specification for silicon dioxide (E551) describes only the process by which SiO_2 may be produced for

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foods and amending Council Regulation (EEC) No 1576/89, Council Regulation (EEC) No 1601/91, Regulation (EC) No

[25] Enzymes: COM/2006/0425 final - Proposal for a Regulation of the European Parliament and of the Council on food enzymes and amending Council Directive 83/417/EEC, Council Regulation (EC) No 1493/1999, Directive 2000/13/EC, and Council Directive 2001/112/EC {SEC(2006) 1044} {SEC(2006) 1045}

[26] Common authorisation procedure: COM/2006/0423 final - Proposal for a Regulation of the European Parliament and of the Council establishing a common authorisation procedure for food additives, food enzymes and food flavourings.

food additive use i.e. no definitions for source materials are prescribed. However, the source compounds for SiO_2 used in the production of the nanoscale SiO_2 coatings in the example (section 2.2.2), includes organosilicates, silanes, chlorosilanes and tetraethylorthosilane (TEOS). In addition, the current EU purity specification for TiO_2 (E171) does not prescribe criteria related to particle size, which clearly is a principal issue in terms of the use of nanotechnology. This additive was last evaluated in 1977.

6.2 Regulatory Aspects Relating to Nanoscale Food Ingredients

Legislation of particular relevance to nanoscale food ingredients is Regulation (EC) 258/97 concerning Novel Foods and Novel Food Ingredients, which establishes a mandatory pre-market approval system for all novel foods.

A 'novel' food is defined as a food or food ingredient not having a significant history of human consumption within the Community prior to May 1997, and which falls within one of several defined categories. Categories that may have relevance to nanotechnology include "foods and food ingredients with a new or intentionally modified primary molecular structure"; and "foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances".

Considering the current and projected applications of nanotechnologies in food, it is unlikely that most nano-structured food products (at least in the foreseeable future) would fall under the first category, i.e. they would not necessarily have a different molecular structure compared to normal processed food. There is, however, a strong likelihood that they would fall under the second category *providing that* the attached caveat is fulfilled. The onus for recognising that a food substance falls under the latter category, and alerting the competent food assessment body, lies with the person responsible for placing the product on the market. However, in the case of nano-structured foods, Regulation (EC) 258/97 would only appear to be applicable if a substance was regarded both as 'novel' *and* its nutritional value, metabolism or level of undesirable substances was substantially altered compared to its macro-scale counterpart. If a company responsible for placing a nanofood product on the market did not recognise it to be novel (e.g. because the ingredients already have a history of use at the macro-scale), and/or did not consider the properties of the nanofood to be substantially different from its macro-scale counterpart (e.g. because of a lack of information to the contrary, or the lack of a precise definition of the term 'substantially altered'), then it is possible that a safety evaluation under (EC) 258/97 will not be carried out. Thus, the caveat attached to the definition of this category of novel foods may lead to an uncertainty over whether a nano-structured food product would fall under this category, or would be required to test to show that their nutritional value, metabolism or level of undesirable substances have not been affected. It is also not clear whether this regulatory framework would apply to food ingredients that *have* a significant history of use, but may already be marketed in forms that contain particle sizes of 100 nm or less. This is where clarity is required in the wording of the definition for this category of novel foods in relation to nano-structured foods.

A review of the Novel Foods Regulation is currently underway, and this may be a useful opportunity to reappraise its applicability in terms of particle size and the use of nanotechnology. It would also assist both applicants and Competent Authorities if EC Recommendation 97/618 (which provides the framework under which the scientific assessment of genuinely novel foods is performed) was reviewed in parallel, with a view to clearly defining the term 'significant changes' and providing additional guidance to risk assessors in respect of particle size, including prior knowledge of individual substances and their approval and use in other parts of the world.

The other relevant regulatory frameworks applicable to the use of nano food ingredients or additives include the general safety articles of the EU Food Law Regulation (178/2002), which require that food placed on the market is not unsafe. However, in this case it is not clear who will be responsible for ensuring that the foods placed on the market are safe. The traceability of nanomaterials used as food ingredients or additives is also covered under the existing requirements of Regulation 178/2002.

6.3 The Precautionary Principle in Relation to Nanofood

In the absence of detailed toxicological data, but in view of the potential of some nanoparticles to cause harm, it is also appropriate to consider application of precautionary principle (PP) for applications of nanotechnology in food. The PP is a well-accepted tenet of international law, and is an attempt to legally codify the maxim "better safe than sorry". Originally applied in the EU in terms of environmental protection, it has since been accepted that its scope is much wider, and can be applied to the protection of human health. In 2000, the EC adopted a Communication on the use of the PP (Communication from the Commission on the precautionary principle', 2000), which provides a reasoned and structured framework for action in the face of scientific uncertainty or absence of scientific consensus. The Communication gives grounds for assigning responsibility for producing the scientific evidence necessary for a comprehensive risk assessment. Recourse to the PP presupposes that potentially harmful effects deriving from a product or process have been identified, and that existing scientific evaluation does not allow the risk to be determined with sufficient certainty.

The PP is also incorporated into EU food law in Article 7 of Regulation 178/2002, which states that where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment. However, although there is emerging evidence to suggest that certain engineered nanoparticles have the potential to cause harm to human health, it is unclear at present whether there is enough scientific basis to invoke the PP in all applications of nanotechnology for food contact materials. A recent IFST report[27]. has recommended that nanoparticles be treated as new, potentially harmful materials, until testing proves their safety (The Institute of Food Science and Technology Report). More research is needed to provide a better understanding of the level of risk, but it would be prudent to consider application of the PP in certain high-risk applications (e.g. where free engineered nanoparticles have been added to food/ drinks, and where such food/ drinks are likely to consumed in large quantities and/or by a large proportion of the population. Ultimately it is likely to be the responsibility of EFSA and the relevant competent authority to decide on what level of risk is acceptable and whether recourse to this principle is justified. Currently it may be an opportune time to consider the merits of including the PP in the Novel Foods Regulations, given the current review of those regulations.

7.0 Gaps in Knowledge Requiring Further R&D

This study has shown that the available information is currently very sparse in term of experimental data on the toxicology of nanoparticles used as food additives and nanostructured food ingredients, to enable assessment of potential risks to the consumer. Much of the available information on engineered nanoparticles is in relation to inhalation

[27] www.ifst.org/uploadedfiles/cms/store/ATTACHMENTS/ResponseFSA_NanotechnologiesT405app.pdf

toxicology, and there are major gaps in knowledge with regard to the behaviour, fate and effects of nanoparticles via the gastrointestinal route. In our opinion, there is requirement for a considerable amount of basic research into the behaviour of foodstuffs both manipulated or processed at the nanoscale, and into the properties of manufactured nanoparticles that may be introduced into foods either deliberately, or as a result of contamination. In view of the gaps in knowledge identified in this report, a few potential issues have been highlighted below in relation to the needs for further research. At present, many of these remain conceptual, but the development of novel foodstuffs containing manufactured nanoparticles or nanostructures must take into account such possible outcomes.

7.1 Targets for Future Research

- Physicochemical properties of nano-sized food additives, their interactions with other food components, and fate and behaviour in the gastrointestinal tract.
- Potential effects of nano-sized food additives on the function of gastrointestinal tract epithelium and other cells, and on the gut natural microflora.
- The extent of changes in the absorption and bioavailability of nano-additives compared to macro-scale equivalents, the toxicological significance of such changes, and whether they should lead to a lowering of their permissible limits in food.
- Potential effects of nano-sized food ingredients or additives on the nutrient/ metabolite transport in and out of the cell, and whether this could lead to a significant effect on the overall nutrient profile in the body.
- The extent of changes in the composition of foods when processed at nano-scale, and whether they warrant consideration as novel food.
- Potential changes to the way in which food constituents are digested as a consequence of their nanoscale processing; for example, whether the introduction into foods of engineered nanoparticles designed to carry dietary supplements can also lead to introduction of foreign substances into the blood.[28]
- Potential for indirect contamination of food through migration of nanomaterials from food packaging or active surfaces used in food processing.

Interdisciplinary research will be vital in establishing the potential risks of nanotechnology and to controlling them. For example, there is much that can be learned from those areas of medical research looking into the passage of nanoparticles through the gut as a vehicle for targeted drug delivery. Tracking advances in these fields will help to highlight processes that could present a possible issue for application of nanotechnologies in foodstuffs.

[28] As a theoretical example, it is known that engineered nanoparticles below ~40 nm in diameter have a size which is comparable to large proteins. If added to foodstuffs, it is possible that dependent on their surface chemistry, they adsorb or bind dietary proteins (Borm et al., 2005). It is well known that proteins bind to and aid adsorption of certain dietary constituents e.g. vitamins (Berne & Levy, 2000). Therefore, should an introduced nanoparticle form a protein-nanoparticle complex, this could theoretically go on to act as a receptor-agonist within the gut, protect the protein from recognition by digestive enzymes, or (should it be transported through the epithelium with the protein) allow the nanoparticle to interact with other endogenous proteins at the site of deposition (Borm et al., 2005). All of these could have potentially harmful effects on the body.

8.0 Conclusions and a Way Forward

The findings of this study are in agreement with a recent report by Cientifica (2006) that nanotechnology applications in the EU's food industry are at an elementary stage. As with any new technology, most nanotechnology applications for food are likely to be for high-value products in the short term. This study has shown that a number of nanotechnology based food/ supplements/ nutraceuticals are available in some countries. It is also widely anticipated that such applications will start to emerge on the UK/ EU market in the next few years. This, therefore, provides an opportunity to address the main uncertainties and gaps in knowledge ahead of the full-scale emergence of nanofoods in the UK/ EU.

Considering the current uncertainties in relation to the potential risks from nanotechnology applications for food, knowledge gaps, and concerns, there is a need for a proactive approach to address some of the unknowns through research, discussion with key stakeholders, and appropriate revision of regulations to manage the potential risks. It would, however, need a substantial amount of basic research to generate data on the food nanostructures and nanoparticles to enable adequate assessment of risks to an average consumer of nanofoods. As the new phenomenon of nanofood and associated issues are global, all of the questions can not realistically be addressed by UK funded research alone. It is, therefore, suggested that EU FP7 program of funding may be used to address some of the main and priority issues (highlighted in section 7.1), with support funds from the FSA. The proposed research will provide the much-needed data to clear the main uncertainties in current regulatory controls, which (as recommended by the Institute of Food Science and Technology (IFST)) should be clarified through official guidelines in the short term, pending a more permanent resolution of the status of the nanofood products at the EU level[10].

A contentious, but important, issue in this regard is that of the labelling of foodstuffs that are products of nanotechnology, especially where manufactured nanoparticles have been used. This is one of the key issues that requires thorough consideration and consultation with different stakeholders. As mentioned before, it is likely that applications of nanotechnology in agriculture and food are likely to attract significant public concern in the coming years. Like any other new technology, public confidence, trust, and acceptance are likely to be the key factor in determining the success or failure of nanofoods. It would, therefore, be prudent to support stakeholder forums aimed at enabling the industry to adopt a proactive approach to tackling the issues head-on by informing, engaging and consulting consumers at the outset. There is also a need for consultation on declaring the use of nanoparticle ingredients or additives in food products.

Any adjustments to regulatory frameworks will also need to take into account the European/ international dimension as part of the harmonised international efforts to the governance of nanotechnology risks. In this regard, a sensible regulation of this area may not necessarily need any major changes in legislation. However, for the current regulatory frameworks to be effective in controlling the potential risks from application of nanotechnology in food, the relevant legislation should provide a clear definition that encompasses the distinctive properties of nano substances in food, a clearly defined responsibility/ liability for relevant products and applications, and appropriate permissible limits that relate to the (potential) effects of nano substances in food. Although there is not enough scientific knowledge at present to warrant application of the precautionary principle to nanofood, it would be in the industry's own benefit to develop appropriate voluntary initiatives to self-regulate some of the aspects that may carry greater risk than other applications. We believe that FSA can play a key role in facilitating the formation of a suitable industry body that can establish the principles for self-regulation by setting out best practices, and demanding safety assessment and risk-benefit analysis from members prior to product development and marketing. We recommend engaging the food industry in a dialogue to achieve a consensus on the issues highlighted in this report, and develop a partnership between scientific community-

regulators-industry-consumer forums to address some of the areas that need urgent research.

We also recommend that a workshop of relevant stakeholders be sponsored by the FSA, to discuss the findings of this report and get views on the highlighted issues from other international experts.

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Table 1: List of relevant patent applications

Patent Assignee	Application/ Patent reference	Title/ Brief description
Food Processing		
BASF (Germany)*	US5891907 1999-04-06	'Stable aqueous solubilizates are disclosed suitable for parenteral administration, of carotenoids and vitamins or vitamin derivatives, in which the carotenoid and the water-insoluble vitamins are, with the aid of a non ionic emulsifier, in the form of a micellar solution, the micelles being smaller than 100 nm'.
University of Kyoto (Japan)	WPI ACC NO: 2006-502687/200651	'Cello oligosaccharide derivative for nonionic surfactant, comprises hydrophobic moiety of alkylated glucose or cello oligosaccharide bonded in block fashion, and hydrophilic moiety or monosaccharide or oligosaccharide …. For nonionic surfactant and nanoparticles (both claimed) used as food additive or pharmaceutical coating agent …. The cello oligosaccharide derivative has favourable amphiphilic property, high biodegradability and surface active ability'
BASF AG (Germany)	WPI ACC NO: 2006-381584/200639	'Aqueous dispersions for preparation of pharmaceuticals and cosmetics, comprises water soluble or insoluble active substance and protective single-celled organism protein colloid ….. Aqueous dispersion comprising a slightly soluble or water insoluble active substance and a protein as a protective colloid (0.1-99.9 wt%) produced by fermentation of microorganism (mushrooms, yeasts and bacteria) in the form of homogenized biomass, where the dispersion is an emulsion or suspension that contains softener (0.1-70 wt%), emulsifying agent (0.01-70 wt%), antioxidants (0.01-50%) and preservatives and the active substance is nanoparticles (0.1-90 wt%)'.
Medipol SA	WPI ACC NO: 2006-463802/200647	'Hydrophilic particles useful in biological system for transport comprise cationic chitosan derivative and polyanionic polymer …. Hydrophilic particles comprise one type of cationic chitosan derivative (C1) and one type of polyanionic polymer (C2) …. As particles e.g. microparticles and nanoparticles useful in biological system for transport; and in pharmaceutical composition, cosmetic composition, food composition or derma-pharmaceutical composition'.
Medesis Pharma	WPI ACC NO: 2006-322061/200634	'Preparation of reverse micelles with aqueous core useful in e.g. in pharmaceuticals field involves contacting sterol, acyglycerol, water and water-soluble metal cation and stirring obtained mixture by mechanical stirring or sonication….. Preparation of reverse micelles with an aqueous core of <= 100 nm involves contacting a sterol, an acylglycerol (preferably diacylglycerol of fatty acids), water (preferably purified water), and a water-soluble metal cation; and stirring mixture for <= 40 (deg)C mechanically at a speed of 1000 - 5000 revolution/minute or by sonication. The ratio (W) of purified water/acylglycerol is <= 5'
Nestec SA	WPI ACC NO: 2006-263537/200627	'Production of nanoparticulated whey protein for use as emulsifier, fat substitute, whitening and/or filling agents, by adjusting the pH at a very precise narrow range of aqueous solution of whey protein, and heating the aqueous solution….. to obtain a liquid dispersion of spherical nanoparticulated whey protein having a particle size of less than 1 mum …. for use in the preparation of food product, food supplement, nutritional and/or pharmaceutical composition.'.
Simo Nanometer Tech Co Ltd (Canada)	WPI ACC NO: 2006-195329/200621	'Nanometer food granule used as medicine and its application ….. A nanoparticle as both food and medicine with high biologic utilization rate can be used for preparing the health-care food in the form of beverage, oral liquid, jelly, etc'.
3M Innovative Properties CO (USA)	WPI ACC NO: 2006-077842/200608	'Emulsion for use in, e.g. foods, comprises continuous liquid phase containing surface-modified dendrimers dispersed in the continuous phase, and dispersed liquid phase dispersed in the continuous phase ….. For use in foods, cosmetics, or pharmaceuticals ….. The inventive emulsion is stable from days to years constant temperature'.

Wang M. (Canada)	WPI ACC NO: 2005-507272/200552	'Propolis royal jelly health-care food and its production method ….. A health-care food for preventing cardiovascular and cerebrovascular diseases, diabetes and cancer is prepared from royal jelly and propolis through adding VC to royal jelly, freeze drying to become powder, extracting active components from propolis in alcohol, nano-pulverizing, freeze drying to obtain nanoparticles, and proportionally mixing them together'.
Chem Lab Richter GMBH Kurt (Germany)	WPI ACC NO: 2004-679226/	'Use of ester polyol compounds as solvents, or solvent or dispersion aids in production of emulsions or dispersions containing organic compounds, pigments or pharmaceuticals, cosmetics, detergents, food or agrochemical agents ….. Used for production of ester polyol/polyol-in-oil or ester polyol/polyol-in-oil-in-water emulsions or dispersions containing poorly soluble organic compounds, pharmaceuticals, cosmetics, detergent components, agrochemical or pigments ….. The problems associated with prior-art methods are overcome and alternative solid lipid nanoparticle (SLN) systems can be obtained'.
University Greifswald (Germany)	WPI ACC NO: 2004-661875/200464	'Compositions comprising terrestrial mushroom biomass and thiocyanates, e.g. useful as drug carriers, health-promoting products, foods, animal feeds, dietary supplements ….. The mushroom biomass is reduced to micro- and nanoparticles with a diameter of 10 nm to 10 microm'.
Rohm & Haas Co (USA)	WPI ACC NO: 2004-583198/200457	'Crosslinked polymeric nanoparticles for use as carrier materials for skin care and food products, comprises skin care or food ingredients ….. crosslinked polymeric nanoparticles having a diameter of 1-10 nm comprising skin care ingredients and food ingredients'
3M Innovative Properties Co (USA)	WPI ACC NO: 2004-560593/200454	'Emulsions useful in food, cosmetics and pharmaceuticals comprises a continuous liquid phase containing surface-modified organic molecules and/or organic polymeric microspheres ….. An emulsion comprises a continuous liquid phase (P1) containing surface-modified organic molecules (I) dispersed in it and a dispersed liquid phase (P2). (I) Is selected from fullerenes, dendrimers and/or organic polymeric microsphere'.
Biotesys GMBH (Germany)	WPI ACC NO: 2003-877483/200381	'Targeted transport system for active agents in the pharmaceutical, cosmetic and food sectors, especially for micronutrients, comprising hybrid particles containing layer(s) of lipid molecules and peptide ligand(s) ….. The lipid molecule is bonded to the ligand(s) via a spacer unit, specifically formed from amino acids or chemically inert materials such as nanoparticles, carbon nanotubes, nanofibers or colloids'.
Biosante Pharm Inc	WPI ACC NO: 2001-256098/	'Processing milk to separate casein and milk proteins, by contacting with a chelating agent, contacting the clarified milk with insoluble divalent cation salts and separating the solid phase from the liquid phase ….. The IDCS [insoluble divalent cation salts] comprises calcium or magnesium salts, preferably calcium phosphate (especially comprising biodegradable brushite or hydroxyapatite based particles) and/or calcium carbonate, or magnesium carbonate and/or magnesium phosphate. The IDCS are micro particles from 1-10 microm diameter or are nanoparticles of diameter 200-400 nm'.
Andry M., Buffevant C., Coletica SA; Edwards F., Levy M., Pariot N., Perrier E., Rey-Goutenoire S. (France)	WPI ACC NO: 2000-163212/200015	'Micro and nano particles useful e.g. as carriers of medicines, and agrochemicals, absorbents for cosmetic purposes, and for separations and analysis ….. Particles comprise cell walls formed by the crosslinking of one or more mono- or oligosaccharides, using emulsion interfacial crosslinking ….. The particles (0.1-20, preferably 0.1-5, wt. % of the composition) are preferably micro- or nano-particles, especially micro- or nano-capsules or spheres'.
Vesifact AG	WPI ACC NO: 2000-025293/200003	'Nanofood useful in human and animal food and drink, including therapeutic food ….. The end product is a liquid in the form of a mineral water, fruit or vegetable juice, syrup, milk or imitation milk product; a semisolid in the form of a yogurt, curds, margarine, high-fat emulsion, spread, edible ice or mineral water; or a solid in the form of an instant powder. The product contains the nanofood per se or 0.01-60, especially 0.05-20 wt. % nanofood in the aqueous phase ….. nanoparticles remain in suspension or emulsion and do not aggregate ….. the end products are used as food, diet food and for stimulating and improving body functions, prophylaxis, assisting therapy or therapy of diseases; and as drink, food, diet food, energy drink, energy food or functional food'.

Coletica SA	WPI ACC NO: 1999-612251/199953	'Particles for chelating metal ions, useful in cosmetic, pharmaceutical and food products and products for treating liquids, especially water ….. A particle selected from a micro particle and/or a nanoparticle having a surface which comprises, at least on the surface thereof, a wall composed of a mixture of at least one protein and at least one polysaccharide which are cross-linked ….. The particles are useful for binding or releasing metal ions in cosmetic, pharmaceutical and food products and products for treating liquids, especially water'.
Cap-Sulution Nanoscience AG (Germany)*	W004030649A2 2004-04-15	'Micro capsules or nanocapsules containing sparingly water-soluble active agent, useful e.g. for rapid drug release on oral administration, having permeable shell containing polyelectrolyte and counter-ion.'
Central P BV, Naarden (Netherlands) *	W003024583A1 2003-03-27	'Novel Calixarene Based Dispersible Colloidal Systems in the Form of Nanoparticles for medical, biological, veterinary, cosmetic and alimentary use, includes nanoparticles comprising amphiphilically modified calixarene.'
Coletica, Lyons (France)*	US6303150 2001-10-16	'Method for producing nanocapsules with crosslinked protein-based walls nanocapsules thereby obtained and cosmetic, pharmaceutical and food compositions using same'
Kraft Foods (USA)*	EP1355537A1 2003-10-29	'Production of capsules and particles for improvement of food products'
Nutralease, Ltd. (Israel)*	US20030232095 Al 2003-12-18	'The nano-sized concentrates of the present invention enable in an efficient manner the solubilization, transport and dilution of oil-soluble, oil non-soluble or water-soluble nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates. Thus they may be used as efficient vehicles for transport of active materials into the human body.'
Rhodia Chimie, Boulogne-Billancourt Cedex (France)*	WOO3095085Al 2003-11-20	'Colloidal dispersions of calcium phosphate nanoparticles and at least one protein, the size of said nanoparticles ranging between 50 and 300 nm, and the morphology of said nanoparticles being spherical...The invention can be used in the food, cosmetic, pharmacological industries.'
Rohm & Haas (USA)*	EP1447074A2 2004-08-18	'Polymeric nanoparticles in consumer products. Crosslinked polymeric nanoparticles having a diameter of 1-10 nm comprising skin care ingredients and food ingredients.'
SolubestLtd., Rehorot (Israel)*	W003028700A3 2003-04-10	'Water soluble nanoparticles of hydrophilic and hydrophobic active materials: This invention provides a soluble nano-sized particle formed of a core (Water-insoluble lipophilic) compound or hydrophilic compound and an amphiphilic polymer and which demonstrated improved solubility and/or stability. The lipophilic compound within the soluble nano-sized soluble ("Solu-nanoparticles") may consist of pharmaceutical compounds, food additives, cosmetics, agricultural products and veterinary products.'
University of Seville, University of Malaga (Spain)*	W002060591A1 2002-08-08	'Device and method for producing stationary multi-component liquid capillary streams and micrometric and nanometric sized capsules, the diameter of which may range from tens of nanometers to hundreds of microns and to a relatively monodispersed aerosol of electrically charged multi-component droplets generated by rupture of the streams due to capillary instabilities. The device and method can be used in fields such as materials science and food technology, wherever generation and controlled handling of structured micrometric and nanometric sized streams is an essential part of the process.'
NONE*	US20030152629 Al 2003-08-14	'Controlled release system that can encapsulate different flavors, sensory markers, and active ingredients, or combinations of flavors, sensory markers and various active ingredients and release multiple active ingredients in a consecutive manner, one after the other. The controlled delivery system is substantially free-flowing powder formed of solid hydrophobie nanospheres that are encapsulated in moisture sensitive microspheres.'

NONE*	US6197757 2001-03-06	'Particles, especially microparticles or nanoparticles, of crosslink ed monosaccharides and oligosaccharides, processes for their preparation and cosmetic, pharmaceutical or food compositions in which they are present'
Food Additive		
BASF (Germany)*	US5968251 1999-10-19	'Carotenoid preparations in the form of coldwater-dispersible powders are produced by...preparing a molecular-disperse solution of a carotenoid, with or without an emulsifier and/or an edible oil, in a volatile, water-miscible, organic solvent at elevated temperature and adding therein an aqueous solution of a protective colloid, whereupon the hydrophilic solvent component is transferred into the aqueous phase, and the hydrophobic phase of the carotenoid results as nanodisperse phase...'
Park K.H. (Korea)	WPI ACC NO: 2006-489267/200650	'Preparation method antibacterial wheat flour by using silver nanoparticles…… Provided is a method for preparing a wheat flour which has an antibacterial effect, a food rotting preventing effect and an immunity reinforcing effect by employing a silver nanoparticle'.
Cognis IP Management GMBH	WPI ACC NO: 2006-196869/200621	'Production of micro- or nano-particles, especially from lipids and for use in cosmetics, medicaments or foods, involves simultaneously compressing and cooling the gaseous lipid to give an aerosol ….. The particles are used in the production of (i) body-care cosmetics for the skin, hair, nails etc.); (ii) medicaments; and (iii) foods and food additives'
Iwamoto S. (Japan)	WPI ACC NO: 2005-622273/200564	'Anticancer health food for colon and rectal cancer, contains nanoparticle powder of reishi mushroom spore, non chlorella, lignin, catechin, polyphenol, neem, wasabi-, loquat- and stevia-leaves, mixed with bean paste ….. For controlling and suppressing colon cancer, rectal cancer …..preventing metastatis and lymph cancer'.
Sustech GMBH & Co KG (Germany)	WPI ACC NO: 2004-331998/200431	'Chewing gum, for promoting re- and neo-mineralization of dental enamel, contains nanoparticles of hardly soluble calcium salt and/or its composite ….. Chewing gum contains hardly soluble calcium salt (I) and/or its composite, where (I) has a particle size less than 1000 nm'.
Sustech GMBH & Co KG (Germany)	WPI ACC NO: 2004-315975/200429	'Sweet e.g. caramel, dragee, filled sweet or filled chewing gum, promoting dental health, especially for mineralization of dental enamel and dentine, contains nanoparticles of hardly water-soluble calcium salt and/or composite ….. Sweet contains hardly water-soluble calcium (Ca) salt (I) and/or its composite, in which (I) has a particle size less than 1000 nm'.
Cognis Deut GMBH; Cognis IP Management GMBH (Germany)	WPI ACC NO: 2001-137862/200114	'Use of nanoparticulate sterols and sterol esters as hypocholesterolemic additives for food, including mayonnaise, cooking oils, sausages and confectionery ….. Hypocholesterolemic sterols and sterol esters have improved oral resorbability when converted to nanoparticles with a diameter of 10-300 nm'.
Bridgestone Corporation, Tokyo (Japan)*	US6579929 2003-06-17	'Stabilized silica and method of making and using the same: A surface stabilized, non-agglomerated silica is provided... [It] has a size in the nanometer range. The surface stabilized, non-agglomerated silica can be used as an additive in any application that uses silica, such as reinforcing fillers for elastomeric compositions, foods, drugs, dentifrices, inks, toners, coatings and abrasives.'
Cognis Deutschland Gmbh, Dusseldorf (Germany)*	US6352737 2002-03-05	'The use of nano-scale sterols and/or sterol esters with particle diamteres of 10 to 300 nm as food additives and as active substances for the production of hypocholesterolemic agents. The particular fineness of the particles promotes more rapid absorption by the blood serum after oral ingestion by comparison with conventional sterols and sterol esters.'
Gerold, Lukowsld, Julich, Wolf-Dieter, Ulrike Lindequist, Sabine Mundt (Germany)*	DE10310021A1 2003-10-23	'Micro- or nanoparticles of biomass of lipid-containing marine organisms, useful as pharmaceutical or cosmetic active agents or food additives, e.g. for preventing binding of bacteria to skin or tissue.'

Globoasia, L.L.C., Hanover, Md*	US6379712 2002-04-30	'The invention relates to nanosilver-containing antibacterial and antifungal granules ("NAGs"), The NAGs have long lasting inhibitory effect on a broad-spectrum of bacteria and fungi. The NAGs can be used in a variety of healthcare and industrial products... Examples of industrial products include, but are not limited to, food preservatives, water disinfectants, paper disinfectants, construction filling materials (to prevent mold formation)."
Guan-Gzhou Institute Of Chemistry, Chinese Academy Of Sciences (China)*	CN1448427 A 2003-10-15	'Water dispersible nanometer avicel, its prep. and colloid therefrom: The nanometer microcrystal cellulose powder is surface modified nanometer microcrystal cellulose with added hydrophilic colloid in the amount of 5-150 wt% of nanometer microcrystal cellulose and has grain size of 6.3-100 nanometers. During its preparation, hydrophilic colloid is dispersed homogeneously into water dispersed medium of surface modified nanometer microcrystal cellulose and the mixture is then dried and crushed. The nanometer microcrystal cellulose is easy to be water dispersed to form colloid, which is homogeneous and high in gluing strength and has the small size of micro crystal cellulose maintained, so that it has wide and unique application foreground in food production, medicine, papermaking, textile, new material preparation and other fields.'
Henkel Kgaa, Dusseldorf (Germany)*	DE1002794 8A1 2001-12-20	'Production of suspension of undecomposed meltable material used in e.g. the pharmaceuticals, cosmetics, and food industries comprises preparing emulsion from material, liquid phase and surface modifying agent, and cooling'
Mars, Inc. (USA)*	US5741505 1998-04-21	'...A coated edible product comprising... edible material...and a substantially continuous inorganic coating on a surface of the edible material, wherein said coating covers at least a portion of the edible material and said coating has a thickness ranging from 0.0001 to 0.5 microns.'
Qingtian New Material Research & Development Co. (China)*	CN1409966 A 2003-04-16	'An antibacterial nanometer powder without decoloring for food contains nanometer zirconium phosphate particles as carrier and active antibacterial component. Its advantages are small granularity, broad spectrum, high compatibility, stability and antibacterial efficiency, and no poison.'
University College Dublin, National University of Ireland (Ireland)*	W00401669 6A1 2004-02-26	"A method for the manufacture of patterned microparticles comprises immobilizing microparticles, including nanoparticles, to be patterned on a surface of a porous membrane, causing an inorganic or organic coating material which can bind to exposed surfaces of said microparticles... The patterned microparticles produced can be used in wide range of applications in health, information and communication, and sustainable environment such as shelter, clothing, energy, food, transport and security."
Zhang Liwen (China)*	CN1439768 A 2003-09-03	'Nano feather powder and its processing method and use: A nano-class feather down powder used as the functional and health-care additive of food, feed, cosmetics, medicine, or chemical fibers is prepared from the feather down of duck, goose, birds, etc through water washing, screening, shearing pulverizing, immersing in alcohol, centrifugal drying, microwave oscillating, quick cooling, low-temp pulverizing and sieving. Its advantages are no loss of active components, high specific surface area, molecular activity and affinity to human body and higher health-care effect.
Other [Indirect] Applications		
BASF AG (Germany)	WPI ACC NO: 2006-090355/200609	'Liquid pesticide concentrate composition, useful to protect plant and non-living material against harmful pests, comprises organic pesticide compound; organic solvent; non-ionic block copolymer; and optionally non-polymeric surfactants ….. comprises: at least one organic pesticide compound D; at least one organic solvent (A); at least one non-ionic blockcopolymer (E) comprising at least one polyethyleneoxide moiety (PEO) and at least one hydrophobic polyether moiety (poly-3-4C-alkyleneoxid moiety (PAO)); and optionally one or more non-polymeric surfactants'.

Nanoproducts Corp (USA)	WPI ACC NO: 2004-399134/	'Active ingredient for application to fauna and flora, agriculture, horticulture, aquaculture, pet care and recreational gardening, comprises nanoparticles ….. The nanoparticles comprise at least one essential nutrients selected from copper (Cu), zinc (Zn), K, calcium (Ca), iron (Fe), magnesium (Mg), manganese (Mn), cobalt (Co) and sodium (Na), preferably an element selected from Cu, Zn and Ag. The nanoparticle comprises at least one antimicrobial. The nanoparticle has sizes less than nano-solvation diameter. ….. The nanoparticle comprise at least one oxide, metal and/or drug. The nanoparticle are released over time ….. The nanoparticles encourage growth of flora and fauna and inhibit diseases. The nanoparticles enable to enhance the quality of agriculture, horticulture, aquaculture, gardens and pets. ….. The nano-structured nutrients exhibit rapid and easy absorption and broad near uniform distribution without any wastage'.
BASF AG (Germany)	WPI ACC NO: 2006-089828/200609	'Aqueous dispersion containing active material difficult to dissolve or insoluble in water and rice starch as protective colloid useful as a food additive, nutrient supplement, animal fodder, and for pharmaceutical and cosmetic dispersions ….. The dispersion, powder composition, or liquid oil-miscible composition is useful as a food additive, a nutrient supplement, an animal fodder, and for pharmaceutical and cosmetic dispersions ….. The dispersion contains a natural polymer, i.e. rice starch as protective colloid'.
Bringley J.F., Leraf Y.J.F., Patton D.L., Pochan J.M.; Wien R.W.	WPI ACC NO: 2006-249803/200626	'Inhibiting growth of microbes in liquid having specified pH involves providing filter assembly or filter bed assembly that comprises metal-ion sequestering agent and having an inlet and outlet; and causing liquid to pass through the filter ….. For inhibiting growth of microbes in a liquid having a pH of >=2.5; and for filtering a liquid nutrient having a pH of >=2.5 e.g. a beverage'.
Levy E; Selecto Inc. (USA)	WPI ACC NO: 2002-089267/200212	'Filtration media for removing microorganisms and contaminants from drinking water, includes metal oxide nanocrystals ….. The nanoparticles provide filtration media capable of reducing levels of microorganisms, such as bacteria, including those having average particle size of 0.1-1mum, at an efficiency of 99.999%'.
Shefer A., Shefer S.D. (USA)	WPI ACC NO: 2005-394935/200540	'Multi-component moisture activated controlled release delivery system, for delivery to biological surfaces, comprises a plurality of solid nano-particles formed of a hydrophobic material comprising e.g. natural/ synthetic wax and fat ….. (1) is useful for delivery of nano particles to biological surfaces comprising an oral cavity or mucous membranes of various tissues and (A) is useful for treating periodontal disease'.
Buyuktimkin N., Buyuktimkin S., Midwest Res Lab LLC, Yeager J.L. (USA)	WPI ACC NO: 2005-384711/200539	'Antimicrobial or antiviral preservation of liquid-containing composition, comprises dissolving or dispersing hydrocarbyl aminohydrocarbonates and/or aminohydrocarbyl hydrocarbonates ..the dispersion is emulsified, encapsulated or nanoparticulated ... useful as a pharmaceutical, nutraceutical, cosmetic, personal care, veterinary, agricultural or food product composition ….. useful for sanitizing fresh meat, fish, poultry, live plants, non-living plant materials and inanimate objects'.
Eastman Kodak Co (USA)	WPI ACC NO: 2005-722973/200574	'Inhibiting the growth of microbes in liquid nutrient e.g. beverage, involves utilizing a filter assembly having a filter with metal-ion sequestering agent for removing designated metal ion from the liquid ….. the filter assembly has a filter having a metal-ion sequestering agent for removing designated metal ion from the liquid and inlet and an outlet ….. For inhibiting growth of microbes in liquid nutrients e.g. beverage'.
De Sloovere X., Desschans D., Sirejacob G.	WPI ACC NO: 2004-305087/200428	'Composition useful for combating and preventing health problems in human and animals caused by e.g. insect, molluscs, mites comprises hydrophobic silicon nanoparticles ….. A composition comprising "Aerosil R 7200" (RTM; silica) which has a BET surface of 150 m2/g, carbon content of 5 wt.% and average particle size of 10-15 nm'.
Bosch H.W., Cooper E.R., Elan Pharma Int Ltd; McGurk S.L.	WPI ACC NO: 2001-281805/200129	'Nanoparticulate compositions comprising particles of active agent with cationic surface stabilizers are bioadhesive and useful e.g. as pharmaceuticals, cosmetics or agricultural compositions ….. Stable bioadhesive nanoparticulate compositions which adsorb to a biological surface comprise an active agent, with one or more cationic surface stabilizers adsorbed to their surface where the effective average particle size is less than 4000 nm'.

* Source Cientifica

Table 2: Digestion of food

Digestion of Proteins	Prior to contact with the brush border of the gut epithelium, proteins are hydrolysed to peptides and amino acids by pepsins. This occurs mainly within the stomach and upper small intestine. About 15% of protein ingested is hydrolysed in the stomach, and the rest is hydrolysed within the duodenum and small intestine (S.I). Proteases from the pancreas (trypsinogen, chymotrypsinogen and procarboxypeptidase) and brush border peptidases in the duodenum and S.I. break protein down into small peptides and single amino acids (nanoscale sized products). Amino acids are transported across the brush membrane by amino acid (AA) transport proteins, some of which are Na^+ dependant, and others of which are independent depending on their charge. Small peptides (dipeptides and tripeptides) are rapidly transported across the brush membrane of intestinal epithelial cells by a single membrane transport system with broad specificity (i.e. it transports di- and tri- peptides but not tetra or above). Peptide uptake is a secondary active transport mechanism, which is powered by the electrochemical potential difference of H^+ across the membrane. Once inside the epithelial cells, they are further hydrolysed into single amino acids. This prevents any protein constuents greater than a single AAs passing into the hepatic portal vein, the vessel responsible for carrying all blood from the GIT and taking it to the liver.
Digestion of lipids	Lipids are hydrolysed within the stomach and intestine by lipases, breaking them down into their major constituents, fatty acids, 2-monoglycerides and cholesterol. Due to their inherent properties (e.g. hydrophobicity) and the lipophillic nature of the epithelium, direct diffusion of some lipids e.g. fatty acids across the brush membrane of the gastrointestinal epithelia is possible. However, facilitated lipid transport across the membrane also exists, and absorption of lipids occurs via both routes. There is an amount of re-processing of lipids within epithelial cells. This results in the re-structuring of lipid constituents into triglycerides, cholesterol and phospholipids. These are expelled into intercellular spaces and lymph as ‘Chylomicrons’ - lipid droplets 10-1000nm in diameter, coated with phospholipids. Chylomicrons are too large to pass directly through the basal membrane, but they can pass into the lacteals, where fenestrations allow them to pass into the lymph and consequentially the venous circulation (Berne & Levy, 2000).

Digestion of carbohydrates	Carbohydrates are the primary source of energy for the majority of people. Amylose (main vegetable starch) and glycogen (main animal starch) intake varies with culture. Sucrose and lactose are the principal disaccharides in the diet, and glucose and fructose are the main monosaccharides. Starch (a glucose polymer) is broken down by ά-amylase into maltose, maltotriose and ά-limit dextrins (branched oligosaccharides). These oligosaccharides are further broken down by enzymes in the brush border of the duodenum and jejunum. From here, glucose and galactose are competitively taken up against their concentration gradient into cells alongside Na+ through the brush border of the epithelium via a Na^+ powered secondary active transport mechanism called SGLT1 ('Sodium-Glucose Co-Transporter'). Fructose is taken up rapidly by a fructose specific facilitated transporter GLUT5 ('Glucose Transporter 5'). Fructose, glucose and galactose all cross the basolateral membrane of the epithelial cells via a facilitated transport protein, GLUT2 ('Glucose Transporter 2').

Glossary of terms:

Nanotechnology a broad interdisciplinary area of research, development and industrial activity that involves the manufacture, processing, and application of materials that have one or more dimensions of the order of 100 nanometers (nm) or less[29]

Nanotechnologies a multidisciplinary grouping of physical, chemical, biological, engineering, and electronic, processes, materials, applications and concepts in which the defining characteristic is one of size, that is in the order of 100 nanometer (nm) or less.

Nanoscale having one or more dimensions of the order of 100 nm or less [Note: Also referred to as **nanosize** - PAS 71 Steering Group]29

Nanostructured having a structure at the **nanoscale** [PAS 71 Steering Group]29

Nanoparticle particle with one or more dimensions at the **nanoscale** [PAS 71 Steering Group]29. Also referred to as nanoparticulate, although this term is more often used adjectivally. Novel properties that differentiate nanoparticles from the bulk material are typically developed at a critical length scale of under 100 nm.

Nanomaterial material with one or more external dimensions, or an internal structure, on the nanoscale, which could exhibit novel characteristics compared to the same material without nanoscale features [PAS 71 Steering Group]29

Nanofood this recently coined term 'Nanofood' refers to the use of nanotechnology techniques, materials or tools during production, processing, or packaging of food.

Agglomerate group of particles held together by relatively weak forces, including van der Waals forces, electrostatic forces and surface tension[29]

Aggregate group of strongly associated particles that cannot easily be re-dispersed by mechanical means [PAS 71 Steering Group][29]

Engineered nanoparticles manufactured to have specific properties or a specific composition [PAS 71 Steering Group][29]

Colloid substance consisting of particles not exceeding 1 4m dispersed in a fluid

[BS 2955:1993, Glossary of terms relating to particle technology]

Nanocomposite composite in which at least one of the phases has at least one dimension on the **nanoscale** [Pure and Applied Chemistry [10], pp 1985–2007]

Aspect ratio ratio of the longest Feret's diameter of a particle to the shortest perpendicular [Adapted from BS 2955:1993, Glossary of terms relating to particle technology, by PAS 71 Steering Group][29]

[29] British Standard Institute's Publicly Available Specification (PAS 71:2005)

Publications and Presentations

The following presentation, made at different forums, included an element of the study carried out under the current project:

- Chaudhry, Q. (2006) Nanomaterials in Food and Food Contact Materials: Regulatory and Consumer Safety Implications, Presentation at the Food Contact Plastics Conference June 2006 (Brussels).
- Chaudhry, Q. (2006) Nanomaterials in Food and Food Contact Materials: Regulatory and Consumer Safety Implications, Presentation at the Nano and Micro Technologies in the Food and HealthFood Industries, October 2006, Amsterdam.
- Chaudhry Q. (2007) Potential Consumer Safety and Regulatory Issues in Relation to Products and Applications of Nanotechnology for the Food Sector, Presentation at the Nanotoxicology Conference, April 2007, Venice, Italy.
- Chaudhry, Q. (2007) Nanotechnology Applications for the Food Sector and Implications for Consumer Safety and Regulatory Controls, Presentation at the *2007 CSL/JISFAN Joint Symposium on Food Safety and Nutrition – Nanotechnology in Foods and Cosmetics*, June 2007, Greenbelt MD, USA.

The following publications and presentations are currently in the pipeline:

- Chaudhry, Q., Aitken, R., Scotter, M., Blackburn, J., Ross, B., Boxall, A., Castle, L. and Watkins, R. A review of the applications and implications of nanotechnologies for the food sector (manuscript ready for submission).
- A book '*Outlook For Nanotechnologies In Food*' [Chaudhry, Q., Castle, L. and Watkins, R. (Editors)] to be published by the Royal Society of Chemistry in 2008.
- Chaudhry, Q. Applications and implications of nanotechnologies for the food sector, Presentation to be made at the International Food Congress, Istanbul October 2007.